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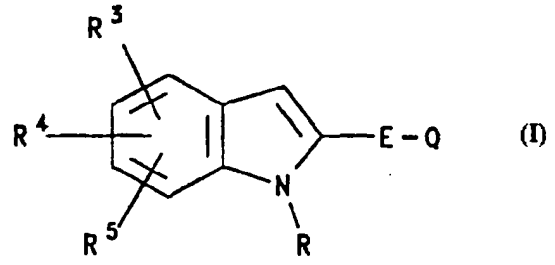
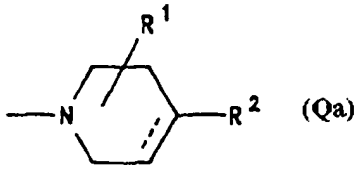
(54) Title: INDOLE DERIVATIVES AS DOPAMINE D4 ANTAGONISTS

(57) Abstract

Compound of formula (I), or a pharmaceutically acceptable salt thereof or a prodrug thereof wherein E represents $-CH_2-$ or $-CH_2CH_2-$; R represents hydrogen or C_{1-6} alkyl; Q represents a moiety of formula Qa, Qb, Qc or Qd which are antagonists of dopamine receptor subtypes within the brain, having a selective affinity for the dopamine D_4 receptor subtype over other dopamine receptor subtypes, and are accordingly of benefit in the treatment and/or prevention of psychotic disorders such as schizophrenia whilst manifesting fewer side-effects than those associated with classical neuroleptic drugs.



(I)



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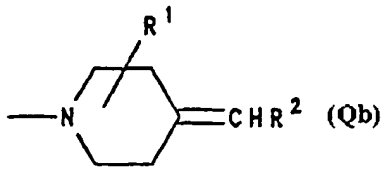
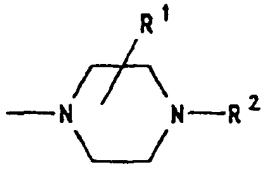
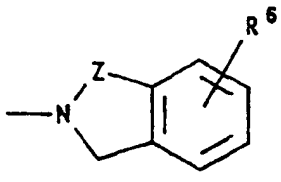


(Qb)



(Qc)



(Qd)

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INDOLE DERIVATIVES AS DOPAMINE D4 ANTAGONISTS

This invention relates to the use of a particular class of heteroaromatic compounds. More particularly, the invention is concerned with the use of substituted indole derivatives which are antagonists of dopamine receptor subtypes within the brain and are therefore of benefit in the treatment and/or prevention of psychotic disorders such as schizophrenia.

The "dopamine hypothesis" of schizophrenia predicts an increased activity of dopamine neurotransmission in the disease. The hypothesis is supported by early observations that drugs, such as amphetamine, with dopamine agonist or dopamine-releasing properties are capable of eliciting a psychosis indistinguishable from acute paranoid schizophrenia.

Schizophrenia is a disorder which is conventionally treated with drugs known as neuroleptics. In the majority of cases, the symptoms of schizophrenia can be treated successfully with so-called "classical" neuroleptic agents such as haloperidol. Classical neuroleptics generally are antagonists at dopamine D_2 receptors. The fact that classical neuroleptic drugs have an action on dopamine receptors in the brain thus lends credence to the "dopamine hypothesis" of schizophrenia.

Molecular biological techniques have revealed the existence of several subtypes of the dopamine receptor. The dopamine D_1 receptor subtype has been shown to occur in at least two discrete forms. Two forms of the D_2 receptor subtype, and at least one form of the D_3 receptor subtype, have also been discovered. More recently, the D_4 (Van Tol et al., Nature (London), 1991, 350, 610) and D_5 (Sunahara et al., Nature (London), 1991, 350, 614) receptor subtypes have been described.

Notwithstanding their beneficial antipsychotic effects, classical neuroleptic agents such as haloperidol are frequently responsible for eliciting acute extrapyramidal symptoms and neuroendocrine disturbances. These side-effects, which clearly detract from the clinical desirability of classical neuroleptics, are believed to be attributable to D_2 receptor blockade in the striatal region of the brain. It is considered (Van Tol et al., supra) that compounds which can interact selectively with the dopamine D_4 receptor subtype, whilst having a less-pronounced action at the D_2 subtype, might be free from, or at any rate less prone to, the side-effects associated with classical neuroleptics, whilst at the same time maintaining a beneficial level of antipsychotic activity.

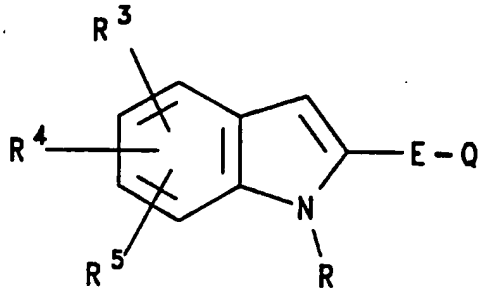
The compounds of use in the present invention, being antagonists of dopamine receptor subtypes within the brain, are accordingly of benefit in the treatment and/or prevention of psychotic disorders such as schizophrenia. Moreover, the compounds of use in the invention have a selective affinity for the dopamine D_4 receptor subtype over other dopamine receptor subtypes, in particular the D_2 subtype, and can therefore be expected to manifest fewer side-effects than those associated with classical neuroleptic drugs.

US Patent 3188313 describes inter alia certain 1-[(2-indolyl)-lower-alkyl]-4-substituted-piperazines, which are alleged therein to possess a panoply of depressant actions on the central and autonomic nervous system, the cardiovascular system and the skeletal-muscular system, including blood pressure lowering, vomiting incidence decreasing, sleeping time potentiating, tranquilizing and skeletal muscle relaxing activities. They are consequently alleged to be useful as hypotensive agents, antinauseants, antipyretics, sedatives, tranquilizers and skeletal muscle relaxants.

In addition, NL-A-6511642 describes a family of 2-[piperidinoalkyl]-1H-indole derivatives, which are stated therein to have analgesic and muscle relaxant activity.

There is, however, no suggestion in US-3188313 or NL-A-6511642 that the compounds described therein would be of any benefit in the treatment and/or prevention of psychotic disorders such as schizophrenia, still less that in doing so they might be expected to manifest fewer side-effects than those exhibited by classical neuroleptic agents.

The present invention accordingly provides the use of a compound of formula I, or a pharmaceutically acceptable salt thereof or a prodrug thereof:



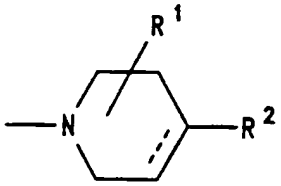
(I)

wherein

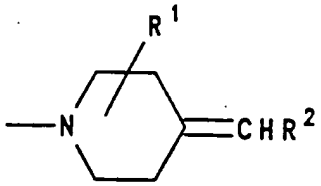
E represents $-CH_2-$ or $-CH_2CH_2-$;

R represents hydrogen or C_{1-6} alkyl;

Q represents a moiety of formula Qa, Qb, Qc or Qd:



(Qa)



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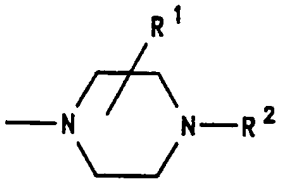

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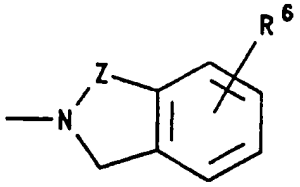


(Qd)

in which the broken line represents an optional chemical bond;

R^1 represents hydrogen, or an optionally substituted C_{1-6} alkyl, C_{1-6} alkoxy, C_{2-6} alkenyl, C_{2-6} alkynyl, aryl, aryl(C_{1-6})alkyl, aryl(C_{1-6})alkoxy, aryl(C_{2-6})alkenyl, aryl(C_{2-6})alkynyl, C_{3-7} heterocycloalkyl(C_{1-6})alkyl, heteroaryl, heteroaryl(C_{1-6})alkyl, heteroaryl(C_{2-6})alkenyl or heteroaryl(C_{2-6})alkynyl group;

R^2 represents an optionally substituted C_{1-6} alkyl, C_{1-6} alkoxy, C_{2-6} alkenyl, C_{2-6} alkynyl, aryl, aryl(C_{1-6})alkyl, aryl(C_{1-6})alkoxy, aryl(C_{2-6})alkenyl, aryl(C_{2-6})alkynyl, C_{3-7} heterocycloalkyl(C_{1-6})alkyl, heteroaryl, heteroaryl(C_{1-6})alkyl, heteroaryl(C_{2-6})alkenyl or heteroaryl(C_{2-6})alkynyl group;

R^3, R^4 and R^5 independently represent hydrogen, hydrocarbon, a heterocyclic group, halogen, cyano, trifluoromethyl, nitro, $-OR^a$, $-SR^a$, $-SOR^a$, $-SO_2R^a$,

$-SO_2NR^aR^b$, $-NR^aR^b$, $-NR^aCOR^b$, $-NR^aCO_2R^b$, $-COR^a$, $-CO_2R^a$ or $-CONR^aR^b$;

Z represents $-CH_2-$ or $-CH_2CH_2-$;

R^6 represents hydrogen, C_{1-6} alkyl, C_{1-6} alkoxy, aryl, aryl(C_{1-6})alkyl or halogen; and

R^a and R^b independently represent hydrogen, hydrocarbon or a heterocyclic group;

for the manufacture of a medicament for the treatment and/or prevention of psychotic disorders such as schizophrenia.

For use in medicine, the salts of the compounds of formula I will be pharmaceutically acceptable salts. Other salts may, however, be useful in the preparation of the compounds of use in the invention or of their pharmaceutically acceptable salts. Suitable pharmaceutically acceptable salts of the compounds of use in this invention include acid addition salts which may, for example, be formed by mixing a solution of the compound of use in the invention with a solution of a pharmaceutically acceptable acid such as hydrochloric acid, sulphuric acid, fumaric acid, maleic acid, succinic acid, acetic acid, benzoic acid, oxalic acid, citric acid, tartaric acid, carbonic acid or phosphoric acid. Furthermore, where the compounds of use in the invention carry an acidic moiety, suitable pharmaceutically acceptable salts thereof may include alkali metal salts, e.g. sodium or potassium salts; alkaline earth metal salts, e.g. calcium or magnesium salts; and salts formed with suitable organic ligands, e.g. quaternary ammonium salts.

The term "hydrocarbon" as used herein includes straight-chained, branched and cyclic groups containing up to 18 carbon atoms, suitably up to 15 carbon atoms, and conveniently up to 12 carbon atoms. Suitable hydrocarbon groups include C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-7} cycloalkyl, C_{3-7} cycloalkyl(C_{1-6})alkyl,

aryl, aryl(C_{1-6})alkyl, aryl(C_{2-6})alkenyl and aryl(C_{2-6})alkynyl.

The expression "a heterocyclic group" as used herein includes cyclic groups containing up to 18 carbon atoms and at least one heteroatom preferably selected from oxygen, nitrogen and sulphur. The heterocyclic group suitably contains up to 15 carbon atoms and conveniently up to 12 carbon atoms, and is preferably linked through carbon. Examples of suitable heterocyclic groups include C_{3-7} heterocycloalkyl, C_{3-7} heterocycloalkyl(C_{1-6})alkyl, heteroaryl, heteroaryl(C_{1-6})alkyl, heteroaryl(C_{2-6})alkenyl and heteroaryl(C_{2-6})alkynyl groups.

Suitable alkyl groups within the scope of the term "hydrocarbon" and within the definition of the substituents R, R^1, R^2 and R^6 include straight-chained and branched alkyl groups containing from 1 to 6 carbon atoms. Typical examples include methyl and ethyl groups, and straight-chained or branched propyl and butyl groups. Particular alkyl groups are methyl, ethyl, n-propyl, isopropyl and t-butyl.

Suitable alkenyl groups within the scope of the term "hydrocarbon" and within the definition of the substituents R^1 and R^2 include straight-chained and branched alkenyl groups containing from 2 to 6 carbon atoms. Typical examples include vinyl and allyl groups.

Suitable alkynyl groups within the scope of the term "hydrocarbon" and within the definition of the substituents R^1 and R^2 include straight-chained and branched alkynyl groups containing from 2 to 6 carbon atoms. Typical examples include ethynyl and propargyl groups.

Suitable cycloalkyl groups include groups containing from 3 to 7 carbon atoms. Particular cycloalkyl groups are cyclopropyl and cyclohexyl.

Particular aryl groups within the scope of the term "hydrocarbon" and within the definition of the substituents R^1, R^2 and R^6 include phenyl and naphthyl.

Particular aryl(C_{1-6})alkyl groups within the scope of the term "hydrocarbon" and within the definition of the substituents R^1, R^2 and R^6 include benzyl, naphthylmethyl, phenethyl and phenylpropyl.

Suitable heterocycloalkyl groups include azetidinyl, pyrrolidyl, piperidyl, piperazinyl, morpholinyl and tetrahydrofuryl groups.

A particular C_{3-7} heterocycloalkyl(C_{1-6})alkyl group within the scope of the expression "a heterocyclic group" and within the definition of the substituents R^1 and R^2 is tetrahydrofurylethyl.

Suitable heteroaryl groups within the scope of the expression "a heterocyclic group" and within the definition of the substituents R^1 and R^2 include pyridyl, quinolyl, isoquinolyl, pyridazinyl, pyrimidinyl, pyrazinyl, pyranyl, furyl, benzofuryl, dibenzofuryl, thienyl, benzthienyl, indolyl, indazolyl, imidazolyl, benzimidazolyl, oxadiazolyl and thiadiazolyl groups.

Particular heteroaryl(C_{1-6})alkyl groups within the scope of the expression "a heterocyclic group" and within the definition of the substituents R^1 and R^2 include thienylmethyl, pyridylmethyl, pyrimidinylmethyl and pyrazinylmethyl.

The hydrocarbon and heterocyclic groups, as well as the substituents R^1 and R^2, may in turn be optionally substituted by one or more groups selected from C_{1-6} alkyl, adamantyl, phenyl, aryl(C_{1-6})alkyl, halogen, C_{1-6} haloalkyl, C_{1-6} aminoalkyl, trifluoromethyl, hydroxy, C_{1-6} alkoxy, aryloxy, keto, C_{1-3} alkylenedioxy, nitro, cyano, carboxy, C_{2-6} alkoxycarbonyl, C_{2-6} alkoxycarbonyl(C_{1-6})alkyl, C_{2-6} alkylcarbonyloxy, arylcarbonyloxy, C_{2-6} alkylcarbonyl, arylcarbonyl, C_{1-6} alkylthio, C_{1-6} alkylsulphinyl, C_{1-6}

alkylsulphonyl, arylsulphonyl, trifluoromethane-sulphonyloxy, $-NR^VR^W$, $-NR^VCOR^W$, $-NR^VCO_2R^W$, $-NR^VSO_2R^W$, $-CH_2NR^VSO_2R^W$, $-NHCONR^VR^W$, $-PO(OR^V)(OR^W)$, $-CONR^VR^W$, $-SO_2NR^VR^W$ and $-CH_2SO_2NR^VR^W$, in which R^V and R^W independently represent hydrogen, C_{1-6} alkyl, aryl or aryl(C_{1-6})alkyl.

The term "halogen" as used herein includes fluorine, chlorine, bromine and iodine, especially chlorine.

The present invention includes within its scope the use of prodrugs of the compounds of formula I above. In general, such prodrugs will be functional derivatives of the compounds of formula I which are readily convertible <u>in vivo</u> into the required compound of formula I. Conventional procedures for the selection and preparation of suitable prodrug derivatives are described, for example, in "Design of Prodrugs", ed. H. Bundgaard, Elsevier, 1985.

Where the compounds of use in the invention have at least one asymmetric centre, they may accordingly exist as enantiomers. Where the compounds of use in the invention possess two or more asymmetric centres, they may additionally exist as diastereoisomers. It is to be understood that the use of all such isomers and mixtures thereof is encompassed within the scope of the present invention.

Suitably, the substituent R represents hydrogen or methyl, especially hydrogen.

Suitably, the substituent R^1 represents hydrogen.

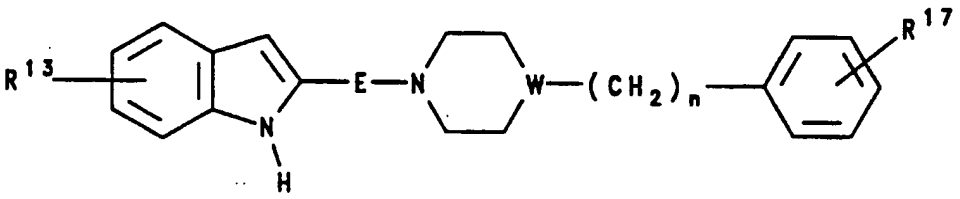
Suitable values for the substituent R^2 include C_{1-6} alkyl, phenyl, halophenyl, C_{1-6} alkylphenyl, C_{1-6} alkoxyphenyl, nitrophenyl, benzyl, halobenzyl, phenethyl, phenylpropyl and benzyloxy. Particular values of R^2 include methyl, ethyl, n-propyl, isopropyl, phenyl, chlorophenyl, ethylphenyl, methoxyphenyl, nitrophenyl,

benzyl, chlorobenzyl, phenethyl, phenylpropyl and benzyloxy.

Suitable values for the substituents R^3, R^4 and R^5 include hydrogen, halogen, cyano, nitro, trifluoromethyl, amino, C_{1-6} alkylamino, di(C_{1-6})alkylamino, C_{1-6} alkyl, C_{1-6} alkoxy, aryl(C_{1-6})alkoxy and C_{2-6} alkylcarbonyl. Particular values include hydrogen, fluoro, chloro, methyl, methoxy and benzyloxy.

Particular values of R^6 include hydrogen, phenyl, chloro and bromo.

A particular sub-class of compounds of use in the invention is represented by the compounds of formula IIA, and pharmaceutically acceptable salts thereof and prodrugs thereof:



(IIA)

wherein

E is as defined with reference to formula I above;

n is zero, 1, 2 or 3;

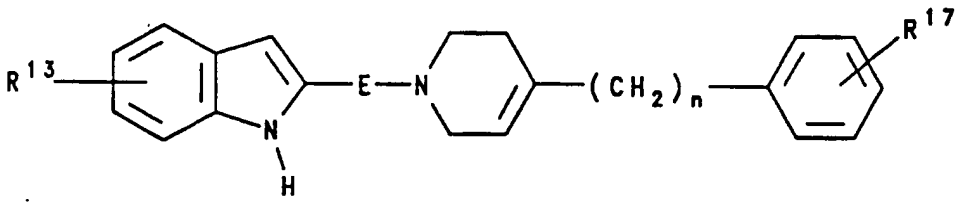
W is CH or nitrogen; and

R^{13} and R^{17} independently represent hydrogen, halogen, cyano, nitro, trifluoromethyl, amino, C_{1-6} alkylamino, di(C_{1-6})alkylamino, C_{1-6} alkyl, C_{1-6} alkoxy, aryl(C_{1-6})alkoxy or C_{2-6} alkylcarbonyl.

Particular values of R^{13} include hydrogen, fluoro, chloro, methyl, ethyl, methoxy and benzyloxy.

Particular values of R^{17} include hydrogen, chloro, methoxy and nitro.

Another sub-class of compounds of use in the invention is represented by the compounds of formula IIB, and pharmaceutically acceptable salts thereof and prodrugs thereof:



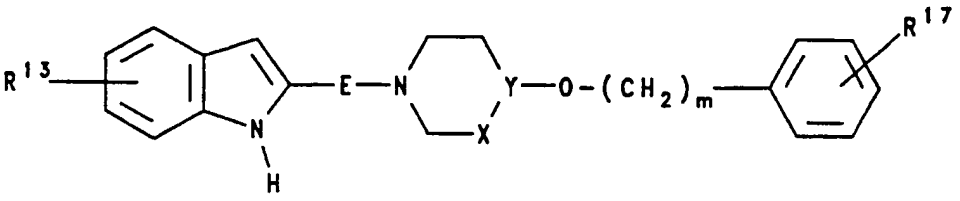
(IIB)

wherein

E is as defined with reference to formula I above; and

n, R^{13} and R^{17} are as defined with reference to formula IIA above.

A further sub-class of compounds of use in the invention is represented by the compounds of formula IIC, and pharmaceutically acceptable salts thereof and prodrugs thereof:



(IIC)

wherein

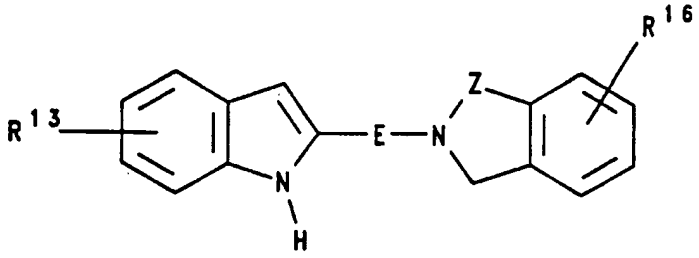
m is 1, 2 or 3;

-X-Y- represents $-CH_2CH-$ or $-CH=C-$;

E is as defined with reference to formula I above; and

R^{13} and R^{17} are as defined with reference to formula IIA above.

A still further sub-class of compounds of use in the invention is represented by the compounds of formula IID, and pharmaceutically acceptable salts thereof and prodrugs thereof:



(IID)

wherein

E is as defined with reference to formula I above;

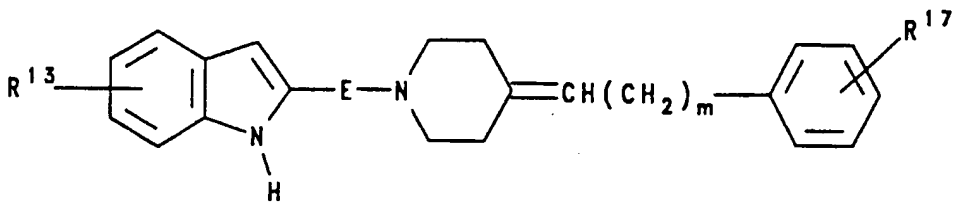
Z represents $-CH_2-$ or $-CH_2CH_2-$;

R^{13} is as defined with reference to formula IIA above; and

R^{16} represents hydrogen, C_{1-6} alkyl, C_{1-6} alkoxy, aryl, aryl(C_{1-6})alkyl or halogen.

Particular values of R^{16} include hydrogen, phenyl, chloro and bromo, especially hydrogen.

A yet further sub-class of compounds of use in the invention is represented by the compounds of formula IIE, and pharmaceutically acceptable salts thereof and prodrugs thereof:



(IIE)

wherein

E is as defined with reference to formula I above;

R^{13} and R^{17} are as defined with reference to formula IIA above; and

m is 1, 2 or 3.

Specific compounds of use in the present invention include:

2-(4-phenylpiperazin-1-ylmethyl)-1H-indole;

2-[4-(4-chlorophenyl)piperazin-1-ylmethyl]-1H-indole;

and pharmaceutically acceptable salts thereof and prodrugs thereof.

Certain compounds falling within the definition of formula I above are novel. Particular sub-classes of novel compounds in accordance with the present invention comprise the compounds of formulae IIB, IIC, IID and IIE as defined above, and salts and prodrugs thereof. The invention further provides a novel compound selected from the following:

2-(4-benzylpiperazin-1-ylmethyl)-1H-indole;

2-[2-(4-benzylpiperazin-1-yl)ethyl]-1H-indole;

2-[4-(4-methoxyphenyl)piperazin-1-ylmethyl]-1H-indole;

2-(4-phenyl-1,2,3,6-tetrahydropyrid-1-ylmethyl)-1H-indole;

2-[4-(2-phenylethyl)piperidin-1-ylmethyl]-1H-indole;

2-(4-benzyloxypiperidin-1-ylmethyl)-1H-indole;

2-[4-(2-phenylethyl)-1,2,3,6-tetrahydropyrid-1-ylmethyl]-1H-indole;
2-[4-(3-phenylpropyl)-1,2,3,6-tetrahydropyrid-1-ylmethyl]-1H-indole;
2-[4-(3-phenylpropylidene)piperidin-1-ylmethyl]-1H-indole;
2-(1,2,3,4-tetrahydroisoquinolin-2-ylmethyl)-1H-indole;
2-(1,2-dihydroisoindol-2-ylmethyl)-1H-indole;
and salts and prodrugs thereof.

The invention also provides pharmaceutical compositions comprising one or more of the novel compounds according to the invention in association with a pharmaceutically acceptable carrier. Preferably these compositions are in unit dosage forms such as tablets, pills, capsules, powders, granules, sterile parenteral solutions or suspensions, metered aerosol or liquid sprays, drops, ampoules, auto-injector devices or suppositories; for oral, parenteral, intranasal, sublingual or rectal administration, or for administration by inhalation or insufflation. Alternatively, the compositions may be presented in a form suitable for once-weekly or once-monthly administration; for example, an insoluble salt of the active compound, such as the decanoate salt, may be adapted to provide a depot preparation for intramuscular injection. For preparing solid compositions such as tablets, the principal active ingredient is mixed with a pharmaceutical carrier, e.g. conventional tableting ingredients such as corn starch, lactose, sucrose, sorbitol, talc, stearic acid, magnesium stearate, dicalcium phosphate or gums, and other pharmaceutical diluents, e.g. water, to form a solid preformulation composition containing a homogeneous mixture of a compound of the present invention, or a pharmaceutically acceptable salt thereof. When referring to these preformulation compositions as homogeneous, it is meant

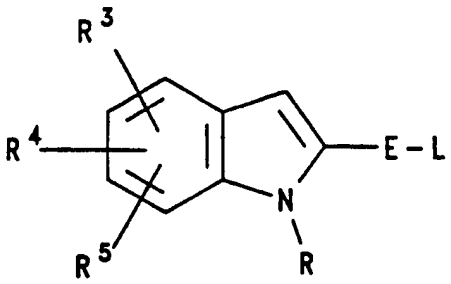
that the active ingredient is dispersed evenly throughout the composition so that the composition may be readily subdivided into equally effective unit dosage forms such as tablets, pills and capsules. This solid preformulation composition is then subdivided into unit dosage forms of the type described above containing from 0.1 to about 500 mg of the active ingredient of the present invention. The tablets or pills of the novel composition can be coated or otherwise compounded to provide a dosage form affording the advantage of prolonged action. For example, the tablet or pill can comprise an inner dosage and an outer dosage component, the latter being in the form of an envelope over the former. The two components can be separated by an enteric layer which serves to resist disintegration in the stomach and permits the inner component to pass intact into the duodenum or to be delayed in release. A variety of materials can be used for such enteric layers or coatings, such materials including a number of polymeric acids and mixtures of polymeric acids with such materials as shellac, cetyl alcohol and cellulose acetate.

The liquid forms in which the novel compositions of the present invention may be incorporated for administration orally or by injection include aqueous solutions, suitably flavoured syrups, aqueous or oil suspensions, and flavoured emulsions with edible oils such as cottonseed oil, sesame oil, coconut oil or peanut oil, as well as elixirs and similar pharmaceutical vehicles. Suitable dispersing or suspending agents for aqueous suspensions include synthetic and natural gums such as tragacanth, acacia, alginate, dextran, sodium carboxymethylcellulose, methylcellulose, polyvinyl-pyrrolidone or gelatin.

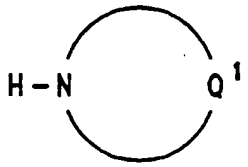
In the treatment of schizophrenia, a suitable dosage level is about 0.01 to 250 mg/kg per day,

preferably about 0.05 to 100 mg/kg per day, and especially about 0.05 to 5 mg/kg per day. The compounds may be administered on a regimen of 1 to 4 times per day.

The compounds of formula I above, including the novel compounds according to the present invention, may be prepared by a process which comprises reacting a compound of formula III with a compound of formula IV:



(III)



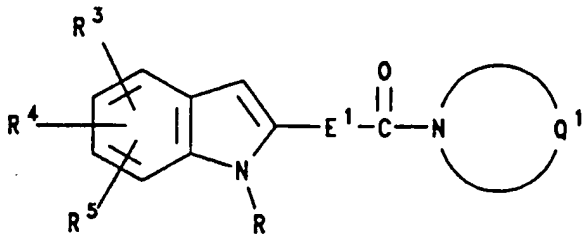
(IV)

wherein E, R, R^3, R^4 and R^5 are as defined above, Q^1 represents the residue of a moiety of formula Qa to Qd as defined above, and L represents a suitable leaving group.

The leaving group L is suitably a halogen atom, e.g. chlorine or bromine.

The reaction is conveniently carried out by stirring the reactants under basic conditions in a suitable solvent, for example potassium carbonate in N,N-dimethylformamide, or triethylamine in tetrahydrofuran or acetonitrile.

In an alternative procedure, the compounds of formula I above, including the novel compounds according to the present invention, may be prepared by a process which comprises reducing a compound of formula V:

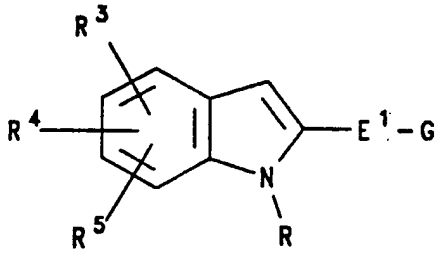


(V)

wherein Q^1, R, R^3, R^4 and R^5 are as defined above; and E^1 represents a bond or a methylene group.

The reaction is conveniently carried out by treating the compound V with a reducing agent such as lithium aluminium hydride in an appropriate solvent, e.g. tetrahydrofuran.

The intermediates of formula V above may suitably be prepared by reacting a compound of formula IV as defined above with a compound of formula VI:



(VI)

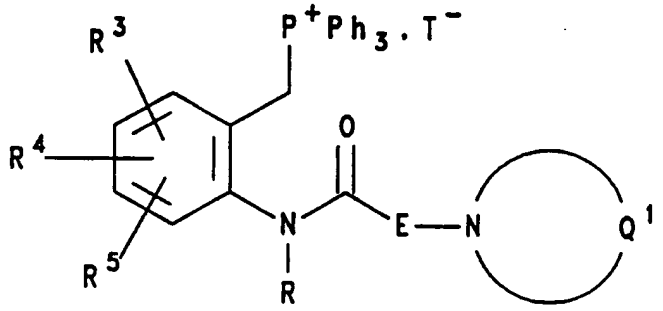
wherein R, R^3, R^4, R^5 and E^1 are as defined above; and G represents a reactive carboxylate moiety.

Suitable values for the reactive carboxylate moiety G include esters, for example C_{1-4} alkyl esters; acid anhydrides, for example mixed anhydrides with C_{1-4} alkanoic acids; acid halides, for example acid chlorides; and acylimidazoles.

By way of example, the intermediates of formula VI above wherein G is an acid chloride moiety may be

prepared by treating the corresponding carboxylic acid derivative with thionyl chloride in toluene. Similarly, the intermediates of formula VI wherein G is an acylimidazole moiety may be prepared by treating the corresponding carboxylic acid derivative with 1,1'-carbonyldiimidazole. Alternatively, the reactive carboxylate moiety G may be obtained by treating the corresponding compound wherein G is carboxy with 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride and 1-hydroxybenzotriazole hydrate, optionally in the presence of triethylamine; the resulting activated carboxylate intermediate may then suitably be reacted in situ with the required compound of formula IV.

In a further procedure, the compounds of formula I above, including the novel compounds according to the invention, may be prepared by a process which comprises the ring closure of a compound of formula VII:



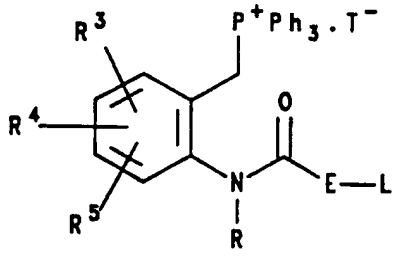
(VII)

wherein R, R^3, R^4, R^5, E and Q^1 are as defined above; and T^- represents a suitable counterion, e.g. a halide ion such as bromide.

The ring closure reaction is conveniently carried out under conditions analogous to those described in Chem. Ber., 1986, 119, 2069-2074. This requires the presence of a strong base, typically potassium t-butoxide; and the reaction is suitably effected in an

inert organic solvent at an elevated temperature, for example toluene at reflux.

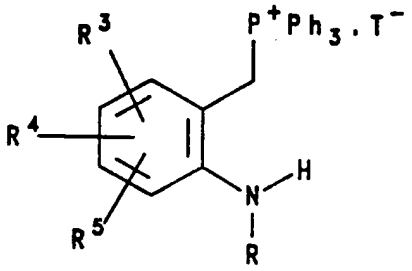
The intermediates of formula VII above may suitably be prepared by reacting a compound of formula IV as defined above with a compound of formula VIII:



(VIII)

wherein R, R^3, R^4, R^5, E, L and T are as defined above.

The intermediates of formula VIII may in turn be conveniently prepared by reacting a compound of formula IX:



(IX)

with an acylating agent of formula G-E-L; wherein R, R^3, R^4, R^5, E, L, G and T are as defined above.

Where they are not commercially available, the starting materials of formula III, IV, VI, IX and G-E-L may be prepared by procedures analogous to those described in the accompanying Examples, or by standard methods well known from the art.

It will be appreciated that any compound of formula I initially obtained from any of the above

processes may, where appropriate, subsequently be elaborated into a further desired compound of formula I using techniques known from the art. For example, a compound of formula I wherein R is hydrogen initially obtained may be converted into a compound of formula I wherein R represents C_{1-6} alkyl by standard alkylation techniques, such as by treatment with an alkyl iodide, e.g. methyl iodide, typically under basic conditions, e.g. sodium hydride in dimethylformamide, or triethylamine in acetonitrile.

Where the above-described processes for the preparation of the compounds of use in the invention give rise to mixtures of stereoisomers, these isomers may be separated by conventional techniques such as preparative chromatography. The compounds may be prepared in racemic form, or individual enantiomers may be prepared either by enantiospecific synthesis or by resolution. The compounds may, for example, be resolved into their component enantiomers by standard techniques such as preparative HPLC, or the formation of diastereomeric pairs by salt formation with an optically active acid, such as (-)-di-p-toluoyl-d-tartaric acid and/or (+)-di-p-toluoyl-l-tartaric acid, followed by fractional crystallization and regeneration of the free base. The compounds may also be resolved by formation of diastereomeric esters or amides, followed by chromatographic separation and removal of the chiral auxiliary.

During any of the above synthetic sequences it may be necessary and/or desirable to protect sensitive or reactive groups on any of the molecules concerned. This may be achieved by means of conventional protecting groups, such as those described in Protective Groups in Organic Chemistry, ed. J.F.W. McOmie, Plenum Press, 1973; and T.W. Greene & P.G.M. Wuts, Protective Groups in Organic Synthesis, John Wiley & Sons, 1991. The

protecting groups may be removed at a convenient subsequent stage using methods known from the art.

The following Examples illustrate the preparation of compounds according to the invention.

The compounds useful in this invention potently inhibit [^{3}H]-spiperone binding to human dopamine D_4 receptor subtypes expressed in clonal cell lines.

[^{3}H]-Spiperone Binding Studies

Clonal cell lines expressing the human dopamine D_4 receptor subtype were harvested in PBS and then lysed in 10 mM Tris-HCl pH 7.4 buffer containing 5 mM $MgSO_4$ for 20 min on ice. Membranes were centrifuged at 50,000g for 15 min at 4°C and the resulting pellets resuspended in assay buffer (50 mM Tris-HCl pH 7.4 containing 5 mM EDTA, 1.5 mM $CaCl_2$, 5 mM $MgCl_2$, 5 mM KCl, 120 mM NaCl, and 0.1% ascorbic acid) at 20 mg/ml wet weight. Incubations were carried out for 60 min at room temperature (22°C) in the presence of 0.05-2 nM [^{3}H]-spiperone or 0.2 nM for displacement studies and were initiated by addition of 20-100 μg protein in a final assay volume of 0.5 ml. The incubation was terminated by rapid filtration over GF/B filters presoaked in 0.3% PEI and washed with 10 ml ice-cold 50 mM Tris-HCl, pH 7.4. Specific binding was determined by 10 μM apomorphine and radioactivity determined by counting in a LKB beta counter. Binding parameters were determined by non-linear least squares regression analysis, from which the inhibition constant K_i could be calculated for each test compound.

The compounds of the accompanying Examples were tested in the above assay, and all were found to possess a K_i value for displacement of [^{3}H]-spiperone from the human dopamine D_4 receptor subtype of below 1.5 μM.

EXAMPLE 1

2-(2-[4-Phenylpiperazin-1-yl]ethyl)indole

Step 1: 2-(3-Chloropropionylamino)benzyltriphenylphosphonium bromide

3-Chloropropionyl chloride (3.0ml, 32mmol) and piperidine (3.5ml, 43.5mmol) were added to a suspension of 2-aminobenzyltriphenylphosphonium bromide (13.0g, 29mmol) (synthesised using the procedure of Capuano *et al*, Chem. Ber., 1986, 119, 2069-2074) in dichloromethane (60ml) under a nitrogen atmosphere. The mixture was heated at reflux for 30 min. and then cooled to room temperature. Dichloromethane (60ml) and hydrochloric acid (1N, 50ml) were added and the precipitated solid was collected by filtration, washed with dichloromethane and dried *in vacuo* to give 2-(3-chloropropionylamino)benzyltriphenylphosphonium bromide (7.5g, 48%). The filtrate was diluted with dichloromethane (300ml) and washed with sodium carbonate (satd., 150ml). Evaporation of the dichloromethane gave a residue which was triturated with ether (200ml) and the white solid collected to afford a second crop of product (5.0g, 32%).

Step 2: 2-(3-[4-phenylpiperazin-1-yl]propionylamino) benzyltriphenylphosphonium bromide

A mixture of 2-(3-chloropropionylamino)benzyltriphenylphosphonium bromide (2.70g, 5mmol) and phenylpiperazine (1.70g, 10mmol) in acetonitrile (85ml) was heated at reflux for 2.5h. The mixture was cooled to room temperature and filtered and the filtrate evaporated *in vacuo* to give 2-(3-[4-phenylpiperazin-1-yl]propionylamino) benzyltriphenylphosphonium bromide as a white solid (3.1g, 93%).

Step 3: 2-(2-[4-Phenylpiperazin-1-yl]ethyl)indole

The phosphonium salt (3.1g, 4.6mmol) was suspended in toluene (150ml) and heated at reflux under Dean-Stark conditions for 90 min. Freshly dried potassium *tert*-butoxide (716mg, 5.5mmol) was added and the mixture was heated at reflux for 30 min. then filtered hot. The cooled filtrate was concentrated *in vacuo* to about 20ml. The residue was dissolved in dichloromethane (100ml) and extracted with hydrochloric acid (1M, 2 x 50ml). The dichloromethane extract was evaporated *in vacuo* and the residue purified by flash chromatography using ethyl acetate as eluant. Recrystallisation from methanol gave the *title compound* as a white solid (18mg, 1.3%), mp 184-186°C; (Found: C, 78.59; H, 7.56; N, 13.50. $C_{20}H_{23}N_3$ requires C, 78.65; H, 7.59; N, 13.76%); δ_H (DMSO-d_6) 2.59-2.61 (4H, m, 2 x piperazinyl CH_2), 2.60 (2H, t, J 4.9Hz, CH_2CH_2N), 2.69-2.73 (2H, m, CH_2CH_2N), 3.14 (4H, t, J 4.9Hz, 2 x piperazinyl CH_2), 6.17 (1H, s, 3-H), 6.76 (1H, t, J 7.2Hz, ArH), 6.78-7.00 (4H, m, ArH), 7.18-7.22 (2H, m, ArH), 7.27 (1H, d, J 8.0Hz, 4-H), 7.39 (1H, d, J 7.6Hz, 7-H), and 10.84 (1H, br s, NH); m/z (CI^+, NH_3) 306 $(M+1)^+$.

EXAMPLE 2

2-(2-[4-Benzylpiperazin-1-yl]ethyl)indole

Step 1: Indole-2-acetic acid

A solution of lithium hydroxide (346mg, 8.25mmol) in water (2ml) was added to methyl indole-2-acetate (520mg, 2.75mmol) (prepared using the method of Capuano *et al*, Chem. Ber., 1986, 119, 2069) in THF (2ml) and methanol (6ml) and the mixture stirred for 1h. The mixture was concentrated *in vacuo*, diluted with water (20ml) and extracted with diethyl ether (2 x 10ml). The aqueous layer was carefully acidified to pH 2 with

1M HCl and extracted into dichloromethane (3 x 20ml). The extracts were dried ($MgSO_4$) and evaporated *in vacuo* to give indole-2-acetic acid (350mg, 72%) as a pink solid.

Step 2: 1-benzyl-4-(2-indolylacetamido)piperazine

1-Hydroxybenzotriazole (324mg, 2.4mmol) and triethylamine (446µl, 3.2mmol) were added to a solution of indole-2-acetic acid (350mg, 2mmol) and 1-benzylpiperazine (352mg, 2mmol) in THF (25ml), followed after 5 min by 1-(3-dimethylaminopropyl)-3-ethyl carbodiimide hydrochloride (576mg, 3mmol) and the mixture stirred for 15 h. The mixture was concentrated *in vacuo* and the residue partitioned between citric acid (1M, 30ml) and ethyl acetate (25ml), the phases were separated and the aqueous layer extracted with ethyl acetate (2 x 25ml). The combined organic layers were washed with sodium bicarbonate (satd., 2 x 10ml) and brine (satd., 20ml), dried (Na_2SO_4) and evaporated *in vacuo* to give 1-benzyl-4-(2-indolylacetamido)piperazine as a pink solid (200mg, 30%), m/z (CI^+, NH_3) 334 $(M+1)^+$.

Step 3: 2-(2-[4-Benzylpiperazin-1-yl]ethyl)indole

Lithium aluminium hydride in ether (1M, 600µl, 0.6mmol) was carefully added to a solution of 1-benzyl-4-(2-indolylacetamido)piperazine (200mg, 0.6mmol) in THF (10ml) and the mixture was stirred at reflux for 1 h. The reaction was cooled in ice and successively treated with water (0.5ml), sodium hydroxide (4M, 0.5ml) and water (1.5ml). The mixture was filtered and the filtrate concentrated *in vacuo*. The residue was purified by column chromatography on silica (90:8:1 CH_2Cl_2/MeOH/NH_3), the resulting gum dissolved in methanol and ether and treated with oxalic acid to give a brown solid (32mg, 11%). M.p. 215-216°C (MeOH); (Found: C, 59.60; H, 5.99;

N, 7.92. $C_{21}H_{25}N_3.2(CO_2H)_2.0.3H_2O$ requires C, 59.47; H, 5.91; N, 8.32%); δ_H (DMSO-d_6) 2.78 (3H, br s, piperazinyl H), 3.06 (7H, m), 3.76 (2H, s, CH_2), 6.22 (1H, s, 3-H), 6.93 (1H, t, J 7.3Hz, ArH), 7.01 (1H, m, ArH), 7.28-7.43 (7H, m, ArH), and 11.01 (1H, br s, NH); m/z (CI^+, NH_3) 320 $(M+1)^+$.

EXAMPLE 3

2-(4-Benzylpiperazin-1-ylmethyl)indole

Step1: 2-(4-benzylpiperazin-1-yl)carbonyl indole hydrochloride

Thionyl chloride (1.62ml, 22.3mmol) was added to a solution of indole-2-carboxylic acid (3.0g, 18.6mmol) in toluene (40ml), the mixture heated at reflux for 3 h and then cooled to room temperature. 1-Benzylpiperazine (3.7ml, 20.4mmol) was added and the resultant precipitate collected by filtration, washed with toluene, and dried *in vacuo* to give 2-(4-benzylpiperazin-1-yl) carbonyl indole hydrochloride (6.5g, 98%). M.p. >210°C (dec).

Step 2: 2-(4-Benzylpiperazin-1-ylmethyl)indole

Lithium aluminium hydride in THF (1M, 11.25mmol) was slowly added to a suspension of 2-(4-benzylpiperazin-1-yl)carbonyl indole hydrochloride (2.0g, 5.6mmol) in THF (40ml) under a nitrogen atmosphere and the resultant solution heated at reflux for 90 min. The mixture was cooled to room temperature and treated sequentially with water (0.5ml), sodium hydroxide (4M, 0.5ml) and water (1.5ml). The mixture was filtered and the filtrate evaporated *in vacuo*. The residue was recrystallised from toluene to afford the *title compound* as a white solid (428mg, 25%), m.p. 157-159°C; (Found: C, 78.44; H,

7.63; N, 13.66. $C_{20}H_{23}N_3$ requires C, 78.65; H, 7.59; N, 13.76%); δ_H (DMSO-d_6) 2.40 (8H, br s, 4 x piperazinyl CH_2), 3.45 (2H, s, CH_2), 3.59 (2H, s, CH_2), 6.23 (1H, s, 3-H), 6.90 (1H, m, ArH), 6.95 (1H, m, ArH), 7.20-7.32 (6H, m, ArH), 7.42 (1H, d, J 7.7Hz, ArH), and 10.93 (1H, br s, NH); m/z (CI^+, NH_3) 306 $(M+1)^+$.

The following were prepared in an analogous manner:

EXAMPLE 4

2-(4-Phenylpiperazin-1-ylmethyl)indole

M.p. 264°C (toluene); (Found: C, 78.68; H, 7.35; N, 14.33. $C_{19}H_{21}N_3$ requires C, 78.32; H, 7.26; N, 14.42%); δ_H (DMSO-d_6) 2.55 (4H, t, J 4.9Hz, 2 x piperazinyl CH_2), 3.14 (4H, t, J 4.9Hz, 2 x piperazinyl CH_2), 3.66 (2H, s, CH_2-N), 6.29 (1H, s, 3-H), 6.75 (1H, t, J 7.3Hz, ArH), 6.89-6.95 (3H, m, ArH), 7.00 (1H, m, ArH), 7.16-7.24 (2H, m, ArH), 7.32 (1H, d, J 7.2Hz), 7.44 (1H, d, J 7.2Hz, ArH), and 11.00 (1H, br s, NH); m/z (CI^+, NH_3) 292 $(M+1)^+$.

EXAMPLE 5

2-(4-[4-Chlorophenyl]piperazin-1-ylmethyl)indole hydrogen oxalate

M.p. 220°C (dec) (MeOH/H_2O); (Found: C, 60.25; H, 5.23; N, 9.67. $C_{19}H_{20}N_3Cl$. $(CO_2H)_2$ requires C, 60.65; H, 5.33; N, 10.10%); δ_H (DMSO-d_6) 2.77 (4H, m, 2 x piperazinyl CH_2), 3.22 (4H, m, 2 x piperazinyl CH_2), 3.91 (2H, s, NCH_2), 6.40 (1H, s, 3-H), 6.93-6.99 (3H, m, ArH), 7.06 (1H, t, J 7.3Hz, ArH), 7.23 (2H, m, ArH), 7.35 (1H, d, J 7.6Hz, 4-H), 7.49 (1H, d, J 7.5Hz, 7-H), and 11.13 (1H, br s, NH); m/z (CI^+, NH_3) 326 $(M+1)^+$.

EXAMPLE 6

2-(4-Phenyl-1,2,3,6-tetrahydropyridin-1-ylmethyl)indole

M.p. 128-130°C (EtOAc); (Found: C, 82.14; H, 6.89; N, 9.46. $C_{20}H_{20}N_2$. $0.25H_2O$ requires C, 82.02; H, 7.06; N, 9.56%); δ_H (DMSO-d_6) 2.48-2.50 (2H, m, $NCH_2C\underline{H}_2$), 2.69 (2H, t, J 5.6Hz, $NC\underline{H}_2CH_2$), 3.11 (2H, d, J 3.0Hz, $NC\underline{H}_2$-CH=), 3.73 (2H, s, $NC\underline{H}_2Ar$), 6.15 (1H, m, NCH_2-C<u>H</u>=), 6.30 (1H, s, 3-H), 6.93 (1H, m, ArH), 6.99-7.04 (1H, m, ArH), 7.23 (1H, t, J 7.2Hz, ArH), 7.29-7.34 (3H, m, ArH), 7.40-7.45 (3H, m, ArH), and 11.03 (1H, br s, NH); m/z (CI^+, NH_3) 289 $(M+1)^+$.

EXAMPLE 7

2-(4-[4-Methoxyphenyl]piperazin-1-ylmethyl)indole hydrogen oxalate

M.p. 218-220°C (dec) (MeOH); (Found: C, 64.55; H, 6.10; N, 9.95. $C_{20}H_{23}N_3O$. $(CO_2H)_2$ requires C, 64.22; H, 6.12; N, 10.21%); δ_H (DMSO-d_6) 2.89 (4H, br s, 2 x piperazinyl CH_2); 3.14 (4H, br s, 2 x piperazinyl CH_2), 3.67 (3H, s, $OC\underline{H}_3$), 4.05 (2H, s, $NC\underline{H}_2Ar$), 6.46 (1H, s, 3-H), 6.81 (2H, d, J 9.1Hz, ArH), 6.90 (2H, d, J 9.1Hz, ArH), 6.99 (1H, t, J 7Hz, indole-H), 7.08 (1H, t, J 7Hz, indole-H), 7.37 (1H, d, J 8Hz, 4-H), 7.51 (1H, d, J 8Hz, 7-H), 11.25 (1H, br s, NH); m/z (CI^+, NH_3) 322 $(M+1)^+$.

EXAMPLE 8

2-(4-[2-Phenylethyl]piperidin-1-ylmethyl)indole hydrogen oxalate

M.p. 230-232°C (dec) (MeOH); (Found: C, 69.98; H, 6.87; N, 6.81. $C_{22}H_{26}N_2$. $(CO_2H)_2$. $0.25H_2O$ requires C, 69.80; H, 6.96; N,

6.78%); δ_H (DMSO-d_6) 1.38 (3H, m, aliphatic H), 1.51 (2H, m, aliphatic H), 1.86 (2H, m, aliphatic H), 2.55 (2H, m, aliphatic H), 2.67 (2H, m, aliphatic H), 3.22 (2H, m, aliphatic H), 4.19 (2H, s, $NC\underline{H}_2Ar$), 6.52 (1H, s, 3-H), 6.98-7.02 (1H, m, ArH), 7.09-7.19 (4H, m, ArH), 7.24-7.28 (2H, m, ArH), 7.40 (1H, d, J 9Hz, 4-H), 7.53 (1H, d, J 8Hz, 7-H), and 11.28 (1H, br s, NH); m/z (CI^+, NH_3) 319 $(M+1)^+$.

EXAMPLE 9

2-(4-[Benzyloxylpiperidin-1-ylmethyl)indole

M.p. 103-105°C (MeOH); (Found: C, 78.33; H, 7.48; N, 8.56. $C_{21}H_{24}N_2O$ requires C, 78.71; H, 7.55; N, 8.74%); δ_H (DMSO-d_6) 1.54 (2H, m, piperidinyl CH_2), 1.85 (2H, m, piperidinyl CH_2), 2.12 (2H, t, J 9Hz, piperidinyl CH_2), 2.71 (2H, m, piperidinyl CH_2), 3.39 (1H, m, piperidinyl CH), 3.57 (2H, s, NCH_2Ar), 4.48 (2H, s, $OC\underline{H}_2Ph$), 6.24 (1H, s, 3-H), 6.92 (1H, m, ArH), 7.00 (1H, m, ArH), 7.23-7.35 (6H, m, ArH), 7.42 (1H, d, J 7.7Hz, 7-H), and 10.94 (1H, br s, NH); m/z (CI^+, NH_3) 321 $(M+1)^+$.

EXAMPLE 10

2-(4-[2-Phenylethyll-1,2,3,6-tetrahydropyridin-1-ylmethyl) indole hydrogen oxalate hemihydrate

M.p. 226-228°C (dec) (MeOH); (Found: C, 69.59; H, 6.23; N, 6.71. $C_{22}H_{24}N_2.(CO_2H)_2.0.5H_2O$ requires C, 69.38; H, 6.55; N, 6.74%), δ_H (DMSO-d_6) 2.27 (4H, m, 2 x CH_2), 2.69 (2H, m, CH_2), 3.04 (2H, br s, CH_2), 3.27 (2H, br s, CH_2), 4.20 (2H, s, $NC\underline{H}_2Ar$), 5.41 (1H, s, $NCH_2\text{-}C\underline{H}$=), 6.51 (1H, s, 3-H), 7.00 (1H, t, J 7.3Hz, ArH), 7.08-7.37 (6H, m, ArH), 7.39 (1H, d, J 8Hz, 4-H), 7.52 (1H, d, J 8Hz, 7-H), and 11.34 (1H, br s, NH); m/z (CI^+, NH_3) 317 $(M+1)^+$.

EXAMPLE 11

2-(4-Phenylpropyl-1,2,3,6-tetrahydropyridin-1-ylmethyl) indole hydrogen oxalate

M.p. 208-210°C (EtOH); (Found: C, 71.27; H, 6.84; N, 6.56. $C_{23}H_{26}N_2$. (CO_2H_2) requires C, 71.41; H, 6.71; N, 6.66%); δ_H (DMSO-d_6) 1.67 (2H, m, $PhCH_2C\underline{H}_2CH_2$), 2.00 (2H, t, J 7.2Hz, CH_2), 2.22 (2H, br s, tetrahydropyridinyl CH_2), 2.54 (2H, t, J 7.6Hz, CH_2), 3.06 (2H, br s, tetrahydropyridinyl CH_2), 3.41 (2H, br s, tetrahydropyridinyl CH_2), 4.24 (2H, s, $NC\underline{H}_2$), 5.39 (1H, s, tetrahydropyridinyl CH), 6.53 (1H, s, 3-H), 7.00 (1H, t, J 7.0Hz, ArH), 7.09-7.19 (4H, m, ArH), 7.26 (2H, t, J 7.3Hz, ArH), 7.39 (1H, d, J 8.0Hz, 4-H), 7.53 (1H, d, J 7.8Hz, 7-H), and 11.38 (1H, br s, NH); m/z (CI^+, NH_3) 331 $(M+1)^+$.

EXAMPLE 12

2-([4-(3'-Phenylpropylidene)piperidin-1-yl]methyl)indole hydrogen oxalate

M.p. 172-174°C ($EtOH/H_2O$); (Found: C, 71.67; H, 6.68; N, 6.74. $C_{23}H_{26}N_2$. $(CO_2H)_2$ requires C, 71.41; H, 6.71; N, 6.66%); δ_H (DMSO-d_6) 2.22-2.26 (6H, m, aliphatic H), 2.56-2.60 (4H, m, aliphatic H), 2.79 (2H, br s, CH_2), 4.08 (2H, s, $NC\underline{H}_2$), 5.24 (1H, t, J 7.1Hz, $PhCH_2CH_2C\underline{H}$), 6.45 (1H, s, 3-H), 6.98-7.20 (7H, m, ArH), 7.39 (1H, d, J 8.1Hz, 4-H), 7.52 (1H, d, J 7.8Hz, 7-H), and 11.29 (1H, br s, NH); m/z (CI^+, NH_3) 331 $(M+1)^+$.

EXAMPLE 13

2-(1,2,3,4-Tetrahydroisoquinolin-2-ylmethyl)indole

M.p. 129-131°C (Me_2CO/H_2O); (Found: C, 81.91; H, 6.87; N, 10.57. $C_{18}H_{18}N_2$. 0.1(H_2O) requires C, 81.84; H, 6.94; N, 10.61%); δ_H ($CDCl_3$) 2.84 (2H, t, J 5.8Hz, $PhCH_2CH_2N$), 2.94 (2H, t, J 5.8Hz, $PhCH_2CH_2N$), 3.69 (2H, s, $PhCH_2N$), 3.89 (2H, s, $ArCH_2N$), 6.41 (1H, t, J 0.9Hz, 3-H), 6.96 (1H, d, J 7.0Hz, ArH), 7.06-7.17 (5H, m, ArH), 7.32 (1H, d, J 8.0Hz, 4-H), 7.57 (1H, d, J 7.6Hz, 7-H), and 8.70 (1H, br s, NH); m/z (CI^+, NH_3) 263 $(M+1)^+$.

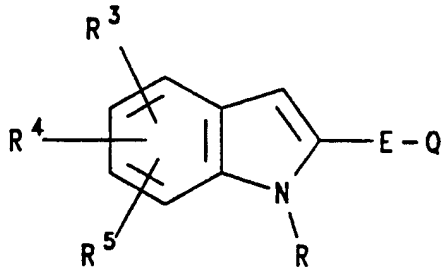
EXAMPLE 14

2-(1,3-Dihydroisoindol-2-ylmethyl)indole

M.p. 176-178°C (dec) ($MeOH/H_2O$); (Found: C, 82.58; H, 6.42; N, 11.13. $C_{17}H_{16}N_2$ requires C, 82.22; H, 6.49; N, 11.28%); δ_H ($CDCl_3$) 3.97 (4H, s, 2 x dihydroisoindolyl CH_2), 4.07 (2H, s, NCH_2Ar), 6.40 (1H, t, J 0.9Hz, 3-H), 7.06-7.22 (7H, m, ArH), 7.28 (1H, dd, J 7.9, 0.8Hz, 4-H), 7.57 (1H, m, 7-H), and 8.64 (1H, br s, NH); m/z (CI^+, NH_3) 249 $(M+1)^+$.

CLAIMS:

1. The use of a compound of formula I, or a pharmaceutically acceptable salt thereof or a prodrug thereof:



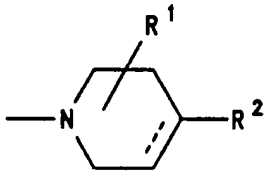
(I)

wherein

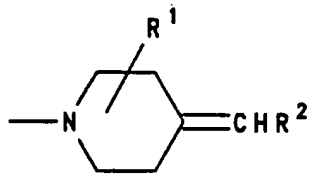
E represents $-CH_2-$ or $-CH_2CH_2-$;

R represents hydrogen or C_{1-6} alkyl;

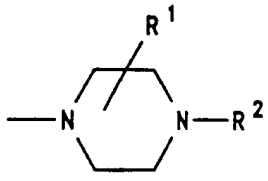
Q represents a moiety of formula Qa, Qb, Qc or Qd:



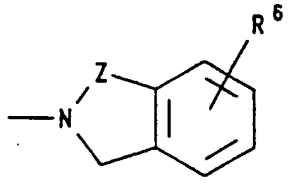
(Qa)



(Qb)



(Qc)



(Qd)

in which the broken line represents an optional chemical bond;

R^1 represents hydrogen, or an optionally substituted C_{1-6} alkyl, C_{1-6} alkoxy, C_{2-6} alkenyl, C_{2-6} alkynyl, aryl, aryl(C_{1-6})alkyl, aryl(C_{1-6})alkoxy, aryl(C_{2-6})alkenyl, aryl(C_{2-6})alkynyl, C_{3-7} heterocycloalkyl(C_{1-6})alkyl, heteroaryl, heteroaryl(C_{1-6})alkyl, heteroaryl(C_{2-6})alkenyl or heteroaryl(C_{2-6})alkynyl group;

R^2 represents an optionally substituted C_{1-6} alkyl, C_{1-6} alkoxy, C_{2-6} alkenyl, C_{2-6} alkynyl, aryl, aryl(C_{1-6})alkyl, aryl(C_{1-6})alkoxy, aryl(C_{2-6})alkenyl, aryl(C_{2-6})alkynyl, C_{3-7} heterocycloalkyl(C_{1-6})alkyl, heteroaryl, heteroaryl(C_{1-6})alkyl, heteroaryl(C_{2-6})alkenyl or heteroaryl(C_{2-6})alkynyl group;

R^3, R^4 and R^5 independently represent hydrogen, hydrocarbon, a heterocyclic group, halogen, cyano, trifluoromethyl, nitro, $-OR^a$, $-SR^a$, $-SOR^a$, $-SO_2R^a$, $-SO_2NR^aR^b$, $-NR^aR^b$, $-NR^aCOR^b$, $-NR^aCO_2R^b$, $-COR^a$, $-CO_2R^a$ or $-CONR^aR^b$;

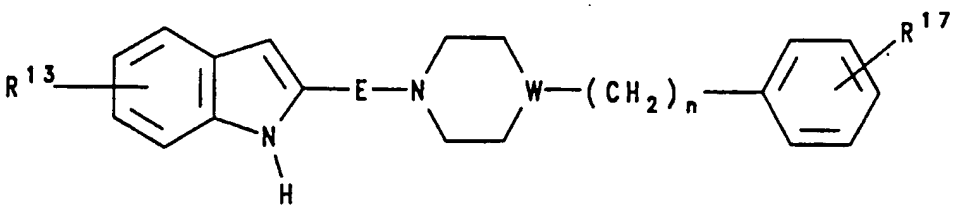
Z represents $-CH_2-$ or $-CH_2CH_2-$;

R^6 represents hydrogen, C_{1-6} alkyl, C_{1-6} alkoxy, aryl, aryl(C_{1-6})alkyl or halogen; and

R^a and R^b independently represent hydrogen, hydrocarbon or a heterocyclic group;

for the manufacture of a medicament for the treatment and/or prevention of psychotic disorders.

2. The use as claimed in claim 1 of a compound represented by formula IIA, and pharmaceutically acceptable salts thereof and prodrugs thereof:



(IIA)

wherein

E is as defined in claim 1;

n is zero, 1, 2 or 3;

W is CH or nitrogen; and

R^{13} and R^{17} independently represent hydrogen, halogen, cyano, nitro, trifluoromethyl, amino, C_{1-6} alkylamino, di(C_{1-6})alkylamino, C_{1-6} alkyl, C_{1-6} alkoxy, aryl(C_{1-6})alkoxy or C_{2-6} alkylcarbonyl.

3. The use as claimed in claim 1 of a compound selected from:
2-(4-phenylpiperazin-1-ylmethyl)-1H-indole;
2-[4-(4-chlorophenyl)piperazin-1-ylmethyl]-1H-indole;
and pharmaceutically acceptable salts thereof and prodrugs thereof.

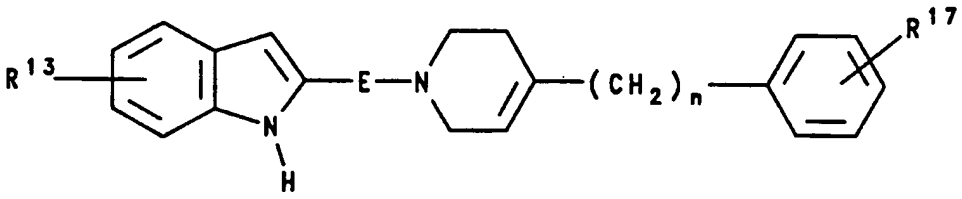
4. A method for the treatment and/or prevention of psychotic disorders, which comprises administering to a patient in need of such treatment an effective amount of a compound of formula I as defined in claim 1, or a pharmaceutically acceptable salt thereof or a prodrug thereof.

5. The method as claimed in claim 4 wherein the compound administered is represented by formula IIA

as defined in claim 2, or a pharmaceutically acceptable salt thereof or a prodrug thereof.

6. The method as claimed in claim 4 wherein the compound administered is selected from:
2-(4-phenylpiperazin-1-ylmethyl)-1H-indole;
2-[4-(4-chlorophenyl)piperazin-1-ylmethyl]-1H-indole;
and pharmaceutically acceptable salts thereof and prodrugs thereof.

7. A compound of formula IIB, or a salt or prodrug thereof:

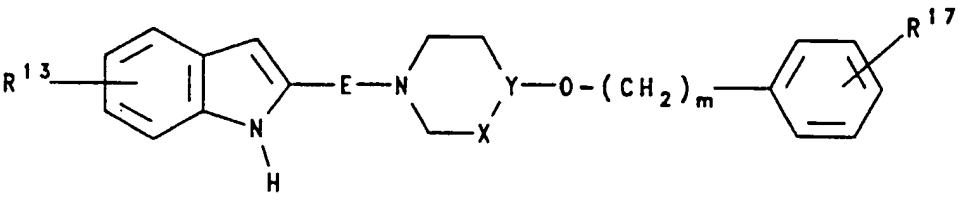


(IIB)

wherein

E is as defined in claim 1; and
n, R^{13} and R^{17} are as defined in claim 2.

8. A compound of formula IIC, or a salt or prodrug thereof:



(IIC)

wherein

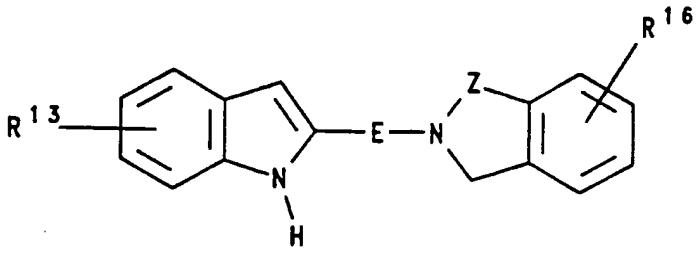
m is 1, 2 or 3;

-X-Y- represents $-CH_2CH-$ or $-CH=C-$;

E is as defined in claim 1; and

R^{13} and R^{17} are as defined in claim 2.

9. A compound of formula IID, or a salt or prodrug thereof:



(IID)

wherein

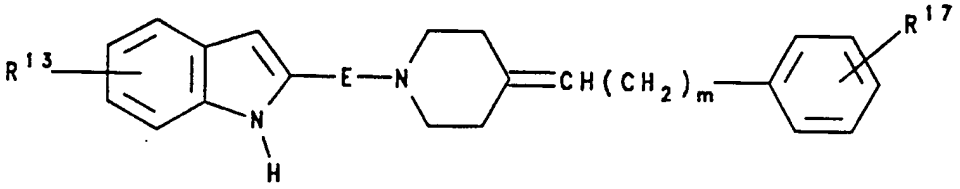
E is as defined in claim 1;

Z represents $-CH_2-$ or $-CH_2CH_2-$;

R^{13} is as defined in claim 2; and

R^{16} represents hydrogen, C_{1-6} alkyl, C_{1-6} alkoxy, aryl, aryl(C_{1-6})alkyl or halogen.

10. A compound of formula IIE, or a salt or prodrug thereof:



(IIE)

wherein

E is as defined in claim 1;
R^{13} and R^{17} are as defined in claim 2; and
m is 1, 2 or 3.

11. A compound selected from:
2-(4-benzylpiperazin-1-ylmethyl)-1H-indole;
2-[2-(4-benzylpiperazin-1-yl)ethyl]-1H-indole;
2-[4-(4-methoxyphenyl)piperazin-1-ylmethyl]-1H-indole;
2-(4-phenyl-1,2,3,6-tetrahydropyrid-1-ylmethyl)-1H-indole;
2-[4-(2-phenylethyl)piperidin-1-ylmethyl]-1H-indole;
2-(4-benzyloxypiperidin-1-ylmethyl)-1H-indole;
2-[4-(2-phenylethyl)-1,2,3,6-tetrahydropyrid-1-ylmethyl]-1H-indole;
2-[4-(3-phenylpropyl)-1,2,3,6-tetrahydropyrid-1-ylmethyl]-1H-indole;
2-[4-(3-phenylpropylidene)piperidin-1-ylmethyl]-1H-indole;
2-(1,2,3,4-tetrahydroisoquinolin-2-ylmethyl)-1H-indole;
2-(1,2-dihydroisoindol-2-ylmethyl)-1H-indole;
and salts and prodrugs thereof.

12. A pharmaceutical composition comprising a compound as claimed in any one of claims 7 to 11 in association with a pharmaceutically acceptable carrier.

13. A compound as claimed in any one of claims 7 to 11 for use in therapy.

14. The use of a compound as claimed in any one of claims 7 to 11 for the manufacture of a medicament for the treatment and/or prevention of psychotic disorders.

15. A method for the treatment and/or prevention of psychotic disorders, which comprises

administering to a patient in need of such treatment an effective amount of a compound as claimed in any one of claims 7 to 11.

INTERNATIONAL SEARCH REPORT

Inter nal Application No
PCT/GB 94/00760

A. CLASSIFICATION OF SUBJECT MATTER
IPC 5 C07D209/14 A61K31/40 C07D401/06

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 5 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	CHEMICAL ABSTRACTS, vol. 66, no. 7, 13 February 1967, Columbus, Ohio, US; abstract no. 28694r, K.T. POTTS ET AL. 'Synthetic experiments related to the indole alkaloids. V. ...' see abstract * RN 102892-13-2 * & J. HETEROCYCL. CHEM. 3(4), 395-401 ---	9
A	EP,A,0 411 631 (MERREL DOW PHARMACEUTICALS INC.) 6 February 1991 see claims ---	1
A	US,A,3 188 313 (STERLING DRUG INC.) 8 June 1965 cited in the application * column 15, line 3-15; claim 21 * -----	1

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
23 June 1994	13. 07. 94

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+ 31-70) 340-2040, Tx. 31 651 epo nl, Fax (+ 31-70) 340-3016	Van Bijlen, H

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/GB94/00760

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 4 - 6 and 15 are directed to a method of treatment of (diagnostic method practised on) the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searches without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

.formation on patent family members

Inter nal Application No
PCT/GB 94/00760

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
EP-A-0411631	06-02-91	AU-B-	625238	02-07-92
		AU-A-	6012390	07-02-91
		CA-A-	2022451	04-02-91
		DE-D-	69008069	19-05-94
		JP-A-	3066683	22-03-91
		US-A-	5064840	12-11-91
US-A-3188313		DE-A-	1445151	09-01-69
		GB-A-	944443	